THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON CANCER SURVIVAL IN THE MULTICENTER AIDS COHORT STUDY AND THE WOMEN'S INTERAGENCY HIV STUDY

by

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ABSTRACT

Objectives: To characterize and compare cancer survival among HIV-infected and –uninfected individuals diagnosed with cancer in the pre-HAART (1984-1994) and the HAART (1995-2013) eras, and to describe cancer survival in the HAART era by HIV status and use of HAART.

Design: A prospective cohort study nested within the Multicenter AIDS Cohort (MACS) and Women's Interagency HIV Study (WIHS).

Study Participants: We studied 911 individuals from the time of cancer diagnosis until the earliest of death or the last study visit attended. Only the initial primary cancers that were diagnosed after enrollment in the MACS or WIHS were included. Second primaries and subsequent metastases were not considered in the analysis. Participants with an unknown cancer diagnosis date were excluded, as were participants with more than a 2-year gap between their last visit prior to cancer diagnosis and the diagnosis date, participants whose SEER Site ICD-0-3 cancer code was an epithelial-cell skin cancer, and those with less than 24 hours of follow-up.

Methods: Cox regression was used to calculate adjusted hazard ratios of death. The proportional hazard assumption was assessed using complementary log-log regression plots and by fitting unadjusted Cox time-dependent Relative Hazards models.

Results: Among MACS participants, HIV-infected individuals with cancers diagnosed in the HAART era compared to those diagnosed in the pre-HAART era had better survival, and the difference between these two groups increased with time following cancer diagnosis. There was no significant difference in survival in the HAART era comparing HIV-infected and HIV-uninfected individuals (adjusted HR: 0.70; 95% CI: 0.35 – 1.38). Survival did not differ for HIV-infected individuals diagnosed with ADMs as compared

to those diagnosed with NADMs in the HAART era, but individuals taking HAART at the visit prior to cancer diagnosis had a lower hazard of death than did those not taking HAART ($p = 0.03$). Interestingly, we also found that HAART use was associated with survival (adjusted HR: 0.36, 95% CI: 0.19 – 0.69) for individuals diagnosed with infection-related cancers, but not among those diagnosed with non-infection-related cancers (adjusted HR: 1.07, 95% CI: 0.67 – 1.72).

Conclusions: The results of this study demonstrate that HAART use prior to diagnosis with infection-related cancers among HIV-infected individuals is associated with improved survival, but this was not the case for non-infection-related cancers. Future research should further assess the survival benefit of HAART for individual infection-related cancers to determine whether our finding is generally relevant for all cancers in this class or for just a select few.

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1.1 Cancer

1.1.1 Background

Cancer refers to a group of heterogeneous diseases of genetic origin that are characterized by uncontrolled cell growth and division that result from mutations in several genes: oncogenes, tumor-suppressor genes, and stability genes (1,2). It is thought that the risk of uncontrolled cell growth and proliferation has been present since the existence of metazoans, and that natural defenses against cancer evolved simultaneously with increased organism complexity (3).

In the United States, an estimated 1.7 million incident cases of cancer were identified in 2014, and cancer remains the second leading cause of death in the United States, following heart disease, with an estimated 585,720 cancers deaths occurring in 2014 (4,5). With increased awareness about risk factors for certain cancers, public health interventions have been successfully implemented, resulting in decreased incidence and mortality rates for certain cancers such as lung cancer (6). However, the incidence for other cancer types, particularly several infection-related cancers (such as liver and oral cancers), remains on the rise (6).

1.1.2 Etiology and Progression

Oncogenes (cancer-inducing genes) become activated when they mutate due to one of three mechanisms (chromosomal translocations, gene amplifications, or certain intragenic mutations) that leads to overexpression (1,3). This activation promotes cell proliferation since, when this occurs, normal signaling is disrupted and oncoproteins release an excess of growth-stimulating signals (3). Conversely, mutations in tumor suppressor genes, whose role it is to regulate cell proliferation, cause gene inactivation

(1,3). Typically, mutations in both copies of a tumor suppressor gene are required to impact the cell phenotype (3). Together, mutations in these two classes of genes contribute to tumor growth and progression by promoting cell birth and preventing cell death (1). Stability genes, such as mismatch repair, nucleotide-excision repair, and base-excision repair genes, repair errors in DNA replication, and thereby reduce the rate of genetic mutations (1). When stability genes are mutated, they become inactivated, and their capacity to repair becomes impaired (1).

Tumorigenesis can be triggered when a mutation in a gatekeeping pathway occurs in a cell that has the capacity to replicate; such a mutation gives the cell a selective proliferative advantage (1). As the majority of cancers have a late onset, with the median age at diagnosis being 66 years, this suggests that tumor progression is a gradual process, and that many cancers require decades to develop (3,5). The transition from a primary tumor to an invasive and metastatic tumor is a multi-stage process called the "the invasion metastasis cascade" that involves breaching the basement membrane, invading the lymphatic or blood microvessels, transportation of cancer cells through the circulatory system, and eventual colonization at another site (3).

1.1.3 Classification and Staging

Cancer classification is based on the histology and the primary site (7). Cancers are classified as carcinomas, sarcomas, myelomas, leukemia, lymphomas or cancers of mixed histology (7). The vast majority of cancers (80 – 90%) are carcinomas, which are malignancies that arise in epithelial tissue or in tissue linings of the body (7).

Cancer staging refers to describing the severity of the disease and is vital for treatment decisions and estimating a patient's prognosis (8). Staging is determined at

diagnosis and involves consideration of the primary site, cell type, lymph node involvement, and tumor size and extent, number (if metastases are present), and grade (8). A commonly used staging system is the TNM system, which describes the primary tumor (T), regional lymph node involvement (N), and the presence of distant metastasis (M) (8). In order to determine staging, patients typically undergo physical exams, imaging studies, lab tests, and, if appropriate, biopsies (8).

1.1.4 Clinical Manifestation and Treatment

Clinical manifestation of cancer comes in many forms. Depending on the primary site, the tumor's growth may lead to pressure on an organ, blood vessel, or nerve, which causes the patient to experience pain (9). Patients may also present with persistent fatigue, fever (usually following metastasis), skin changes, or unexplained weight loss, as the cancer cells consume a large portion of the body's energy resources (9). At times, only after the tumor has become quite large do signs and or symptoms arise (9). Although treatment options vary by cancer type and stage, they typically involve one or more of surgery, radiation, and chemotherapy (10).

1.1.5 Outcomes

Cancer prognosis varies greatly depending on cancer type, stage, treatment, and the response to treatment. At present, the Surveillance, Epidemiology, and End Results program (SEER) estimates that 66.1% of cancer patients (diagnosed with cancers of all sites) in the US survive five or more years after diagnosis; this estimate is based on data gathered during 2004-2010 (5). However, certain cancers, such as pancreatic cancer have extremely poor 5-year survival (6.7%), while others, such as breast cancer, typically, have a much better prognosis (5-year survival: 89.2%) (11,12). Pancreatic cancer survival

is poor since diagnosis often occurs at a more advanced stage, with only 8.8% of cancers being detected when they are localized, as compared to breast cancer which is typically detected earlier (with 61% of cancers detected when they are localized) (11,12). Additionally, in the US, breast cancer is a common cause of cancer mortality among women, and there are screening programs in place to detect breast cancer early (13).

1.1.6 Screening and Prevention

With greater knowledge about the natural history and risk factors for certain cancers, prevention and cancer screening measures have been introduced in an effort to reduce incidence of and mortality due to cancer (14). The US Preventative Services Task Force (USPSTF) evaluates the strength of evidence of interventions and reports its recommendations and the grade (weight of evidence) for certain cancers (15). In reviewing evidence and preparing recommendations, experts consider the potential benefits and harms of screening, the population for which screening would be most appropriate for, and in what settings screening should be implemented (16).

1.1.7 Established Risk Factors for Cancer Incidence and Progression

Many environmental exposures have been associated with an increased risk of certain cancers. Cigarette smoking has been causally associated with numerous cancers, including lung, oral, esophageal, and pancreatic cancer (14). Other important lifestyle factors include nutrition, alcohol use, and physical activity (14). Some cancers are known to be infection-related and infection with certain agents may be necessary for carcinogenesis or may put an individual at increased risk. Infectious agents that have been associated with cancer include human papillomavirus (HPV), Epstein-Barr Virus (EBV), and Hepatitis B and C (14). Radiation exposure (both UV and ionizing) has also

been associated with increased cancer risk (14). Furthermore, immunosuppression has been linked to greater cancer risk (14). Organ transplant recipients and patients living with HIV/AIDS, two populations whose main shared risk factor is immunodeficiency, have been shown to have similar patterns of increased cancer risk (17).

1.2 The Impact of HAART on the Relationship of Cancer and HIV

1.2.1 Introduction

There has been a relationship between cancer and HIV since the start of the Acquired Immunodeficiency Syndrome (AIDS) pandemic, when it was noted that HIV-infected individuals had a higher incidence of three cancers: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and invasive cervical cancer (ICC) (18). Since AIDS was first recognized in the 1980s, an estimated 60 million individuals have been infected with Human Immunodeficiency Virus (HIV) the virus that causes AIDS (19). AIDS has led to the deaths of 25 million individuals, and remains a public health concern as over 33 million individuals worldwide are HIV-infected currently (19). HIV/AIDS research has led to the characterization of HIV and its pathogenesis as well as successful therapeutic interventions, e.g., Highly Active Antiretroviral Therapy (HAART), and strategies to decrease the likelihood of HIV transmission (19). Since the introduction of HAART, trends in cancer incidence among HIV-infected have changed dramatically (18).

1.2.2 Impact of HAART on Cancer Incidence

Introduced in the mid-1990s, HAART has the capacity to alter the natural history of HIV by suppressing HIV replication and to thereby drastically extend the lifespan of seropositive individuals; whereas prior to HAART, once diagnosed with AIDS, individuals typically survived only a few weeks or months following diagnosis, today, a

near-normal life expectancy can often be achieved with HAART initiation earlier in the disease process (19,20). The use of HAART has been associated with dramatic declines in the incidence of the AIDS-defining malignancies (ADMs) KS and NHL and a rise in certain non-ADMs (NADMs) among HIV-infected individuals (20–22). Although HAART has certainly played a substantial role in the changes in cancer incidence observed, it is unclear to what degree its relationship with behavioral risk factors, viral co-infections, and other factors has also contributed to the cancer trends (20). The introduction of HAART has also impacted mortality due to cancer. Whereas in the pre-HAART era cancer-related deaths accounted for 10% of deaths among HIV-infected individuals, at present approximately 30% of all deaths in HIV-infected individuals are cancer-related, which makes cancer prevention and treatment research in this population of great importance (23,24).

In the pre-HAART era, it was noted that certain cancers were more common among individuals living with AIDS. These were KS, NHL, and ICC (23); these cancers became known as ADMs when they arose in seropositive individuals. Studies have shown that "HIV-infected individuals have a 3640-fold increased risk of KS caused by human herpesvirus 8 (HHV8), a 77-fold increased risk of NHL, some of which are caused by Epstein-Barr virus (EBV), and a six-fold increased risk of cervical cancer caused by oncogenic subtypes of human papilloma virus (HPV)" relative to the general population (25). Population-based registry data has been used to estimate cancer incidence prior to and after the introduction of HAART and to assess the impact of HAART on cancer risk in the United States (21). This data showed that in the pre-HAART era, there was a very high incidence of the ADMs KS and NHL, with these

cancers having standardized incidence ratio (SIR) values of 52,900 and 79.8, respectively, for individuals with an AIDS onset during 1980-1989. However, during the early HAART era, there was already a substantial decline in risk relative to the pre-HAART era; the risk of KS and NHL declined by 83.5% and 57.5%, respectively (21). Nonetheless, in the early HAART era (1996-2000), for many cancers, HIV-infected individuals diagnosed with cancer continued to have significantly worse survival relative to individuals in the general population who were diagnosed with cancer (26). Late diagnosis among HIV-infected individuals and opportunistic infections associated with HIV are thought to have contributed to this observed difference in survival (26).

While the introduction of HAART was associated with a decline in the ADMs KS and NHL among HIV-infected individuals, it was also followed by a reported increase in certain NADMs in the HIV-infected population, such as Hodgkin's lymphoma (HL), skin, colorectal, prostate, anal, lung, and renal cancer (22–24). A systematic review of the impact of HAART on cancer incidence among HIV-infected individuals found that there was an overall increased risk of developing NADMs following the introduction of HAART (24). This is in large part because HAART increased the lifespan of seropositive individuals and the risk for most malignancies increases with age (18,22,27). Seropositive individuals have had higher rates of NADMs than the general population does, especially of cancers that are either confirmed or likely to be infection-related (20,28,29). The greater cancer risk in HIV-infected individuals relative to that of the general population may be explained by the higher prevalence of traditional risk factors among seropositive individuals, such as cigarette smoking, viral co-infection (HPV, hepatitis B and C, HHV-8, and EBV), and alcohol use (23,30). It has also been demonstrated that HIV infection is

a risk factor for lung cancer, independent of smoking status (31). Furthermore, even while using HAART, HIV-infected individuals continue to display persistent immunodeficiency, chronic inflammation, and other conditions associated with HIV infection (28,32).

Contrary to prior expectations, studies have not consistently shown an association between HAART use and a decreased risk of NADMs, perhaps because the role of the immunologic response to HAART in the HAART-NADM relationship had not been properly accounted for (33). Much remains to be understood about the mechanism behind the increased risk of certain NADMs and the role of HAART use in cancer survival (28). A recent study began to explore the trends in cancer incidence subsequent to the introduction of HAART using population-level data, and attempted to decipher to what degree these trends are influenced by increased lifespan, temporal trends in the general population, and changes in relative risk in the HIV-infected population (27). This study found that demographic changes as well as temporal trends in the general population had the greatest impact for individuals diagnosed with NADMs (27).

1.2.3 Impact of HAART on Cancer Survival

1.2.3.1 Cancer Survival Comparison by HIV Status and HAART Use

Previous studies have demonstrated that HAART use helped increase short- and medium-term survival among HIV-individuals diagnosed with cancer substantially, and thereby has diminished the difference in survival seen between HIV-infected individuals and the general population during the pre-HAART and early HAART eras (34). A population-based study conducted between 1980 and 2000 comparing the survival of people living with AIDS to that of the general population found that 2-year survival rate

after cancer diagnosis for people living with AIDS showed significant improvement since the introduction of HAART (35). Nonetheless the authors reported that the gap in overall survival between people living with AIDS and the general population persisted (35).

In the case of NHL, some studies have suggested that, in the HAART era, cancer survival is comparable for HIV-infected individuals undergoing cancer treatment while using HAART and HIV–uninfected individuals (36,37). However, many of these studies had a small and very specific study population, and so their results may not necessarily be generalizable (38). A larger prospective cohort study found that HIV-infected individuals had a greater risk of 2-year lymphoma-specific mortality than did the general population, and that survival was only comparable to that of the general population for individuals with a CD4 count of at least 200 cells/μL and no prior AIDS diagnosis (38). This finding should be taken with caution due to the amount of missing CD4 cell count data at the time of cancer diagnosis (38). A recent study also suggested that survival of HIV-infected individuals diagnosed with NHL still lags behind that of HIV-uninfected individuals, even though it has shown substantial improvement (39).

1.2.3.2 Cancer Survival by Cancer Type: ADM vs. NADM

Given the reported synergistic effect of HAART and chemotherapy on survival for individuals with NHL and KS and the direct effect of protease inhibitors (PIs) against KS, we would expect that survival would be better among individuals diagnosed with ADMs as compared to those diagnosed with NADMs (34). It has also been demonstrated that male gender, IDU, co-infection with hepatitis B, earlier year of cancer diagnosis, and non-white race/ethnicity has been associated with worse survival, following an NADM diagnosis (26). The literature available comparing survival of individuals diagnosed with

ADMs to those diagnosed with NADMs has not been conclusive. Two studies have reported that although HAART has improved survival for HIV-infected individuals diagnosed with cancer, overall survival following cancer diagnosis in the HAART era remains poor and does not differ significantly overall among individuals diagnosed with ADMs and those diagnosed with NADMs (34,40). A recent study used an Italian observational cohort to compare survival of seropositive individuals with ADMs to the survival of seropositive individuals with NADMs in the HAART era, and suggested that HAART has less of an effect for individuals diagnosed with NADMs than it does for individuals diagnosed with ADMs (41). It reported that survival two years after diagnosis was comparable in the two groups, but longer-term survival was worse for individuals diagnosed with NADMs, and depended greatly on NADM type (41).

In the case of NHL, simultaneous use of chemotherapy and HAART has been shown to improve response to chemotherapy and increase survival in HIV-infected individuals diagnosed with NHL (42). An exception to the overall increase in survival among HIV-infected individuals diagnosed with NHL was reported in a study examining survival after diagnosis with the aggressive AIDS-related forms of NHL, Burkitt's lymphoma (HIV-BL) and diffuses large-cell lymphoma (HIV-DLCL) (43). This study suggested that while survival has markedly improved in the HAART era for individuals with HIV-DLCL receiving standard chemotherapy, it did not improve for individuals with HIV-BL undergoing standard chemotherapy (43).

2.1.3.3 Cancer Survival by Cancer Type: Infection-related vs. Non-Infection-related

As certain cancers occur much more frequently among HIV-infected individuals, for instance, anal cancer, which is an HPV-related NADM, has an incidence rate 80-110

times greater among HIV-infected men who have sex with men (MSM) relative to the general population, it has become more common to classify cancers as infection-related or infection-unrelated (18). Much remains to be understood about the impact of HAART on infection-related NADMs. HIV-infected individuals are known to have a much higher risk of infection-related NADMs than does the general population (44). This greater risk has been attributed to the higher prevalence of certain viral co-infections (HPV, hepatitis B and C, HHV-8, and EBV) among HIV-infected individuals as well as the limited ability of HIV-infected individuals to suppress the oncogenic viral process as a result of their weakened immune systems (44). As HAART improves immune function, its use may potentially improve control of co-infections, as has already been demonstrated in the case of Hepatitis B clearance (44). This, however, has not been shown to be the case for other infections, and furthermore, is inconsistent with the rise in certain infection-related NADMs seen in the HAART era, such as anal cancer (44,45). Another factor to consider is the timing of HAART initiation, since the ability of HAART to increase CD4 cell count and to thereby improve immune function depends on the level of immune suppression (46). Patients who initiate HAART late and therefore have lower CD4 counts at the time of initiation face persistent inflammation and immunodeficiency and as such are at increased risk for developing and subsequently dying of their cancer (46).

A US multicenter prospective cohort study of HIV-infected individuals in clinical care (CNICS) examined the prognosis of individuals diagnosed with ADMs, infection-related NADMs (where infection-related included squamous cell anal, squamous cell oral/pharynx, HL, liver with viral hepatitis, vaginal, vulvar, and penile), and infection-unrelated NADMs (46). Survival was calculated from the time of cancer diagnosis until

death using an adjusted Cox proportional hazards regression model (46). The adjusted hazard of death was lower for individuals diagnosed with ADMs and infection-related NADMs, both relative to individuals diagnosed with infection-unrelated NADMs (46).

2.1.4 Summary

While the introduction of HAART has certainly had a dramatic impact on the lifespan of seropositive individuals, the actual impact of HAART exposure on cancer mortality is less well characterized, especially since many studies classify individuals' HAART exposure based on calendar year rather than the actual individual HAART exposure. In other words, these studies treat all individuals in the HAART era as exposed to HAART, even though some of them were not, which makes them studies that examine the effectiveness of HAART, rather than its efficacy (19,20,28). Early on, HAART was only being prescribed to the patients who were most ill (guidelines for HAART initiation fluctuated around 200 to 500 cells/μL) and in many instances it was very difficult or impossible to account for the factors associated with initiating HAART (47). As a result, in some study populations HAART users had poorer survival than non-HAART users did because they were sicker. This is less of a concern today since most antiretroviral drugs available are less toxic, have simpler regimens that make adherence more likely, and there is evidence of benefits of earlier HAART initiation, and so many guidelines now promote starting HAART treatment shortly after diagnosis, rather than basing the decision to initiate use on CD4 cell count (47). Our study examined both HAART effectiveness and efficacy, which enabled us to assess how much or little difference there is between the two approaches.

The overarching objective of this study was to examine the effect of HAART on

survival following cancer diagnosis in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) cohorts. Our first aim was to characterize and compare cancer survival among HIV-infected and –uninfected individuals diagnosed with cancer in the pre-HAART (1984-1994) and the HAART (1995-2013) eras. We hypothesized that survival is better among HIV-infected individuals with cancers diagnosed in the HAART era compared to those diagnosed in the pre-HAART era, but poorer than that among HIV-uninfected individuals. Next, we hypothesized that the survival increase in the HAART era among HIV-infected individuals was greater for those diagnosed with ADMs compared to those diagnosed with NADMs. Lastly, we hypothesized that among HIV-infected individuals, the survival increase in the HAART era was greater for infection-related cancers compared to non-infection related cancers.

The second aim of this study was to characterize and compare cancer survival in the HAART era by HIV status and use of HAART. We hypothesized that survival was better among HIV-infected individuals taking HAART at the time of cancer diagnosis than it was among HIV-infected individuals not taking HAART. We also hypothesized that the improved survival among HIV-infected individuals taking HAART was greater for individuals diagnosed with ADMs than it was for individuals diagnosed with NADMs. Finally, we hypothesized that survival was better among HIV-infected individuals taking HAART who were diagnosed with infection-related cancers than it was for individuals diagnosed with non-infection-related cancers.

2. MATERIALS AND METHODS

2.1 Study Population

This study was nested within the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). Details of the MACS and WIHS study designs and populations have been described previously (48–52). In brief, the MACS is an ongoing, multicenter prospective cohort study of HIV-1 infection among homosexual and bisexual men in the United States started in 1984 to examine the natural history of AIDS. Participants were initially recruited from four geographic locations (Baltimore, MD; Chicago, IL; Pittsburgh, PA; and Los Angeles, CA) and follow-up visits occur at six-month intervals. At baseline, data collection included a questionnaire to collect demographic information, past and current medical history, a physical exam, and laboratory tests. The WIHS is an ongoing, multicenter prospective cohort study of women who participate in high-risk behavior for HIV infection in the United States assembled in 1994 in response to the increased incidence of AIDS among women. Participants were initially recruited from six geographic sites (Bronx/Manhattan, NY; Brooklyn, NY; Washington DC; San Francisco/Bay Area; Los Angeles/Southern California/Hawaii; and Chicago, IL) and follow-up visits take place at six-month intervals. Data collection includes interviews (to assess medical history, drug/alcohol use, sexual behavior, and psychological status), a physical exam, and laboratory testing.

2.2 Inclusion/Exclusion Criteria

To generate our study population, we began identifying all confirmed cancers that were documented in the MACS and WIHS through October 2013, and then applied the exclusion criteria as summarized in Figure 1. Specifically, we included only the initial primary cancers that were diagnosed after enrollment in the MACS or WIHS; second

primaries and subsequent metastases were excluded. The date of cancer diagnosis was required in order to evaluate survival time, so we excluded participants with an unknown cancer diagnosis date. Among these participants, we included those with no more than a two-year gap between their last visit prior to cancer diagnosis and the diagnosis date. We excluded participants whose cancer was diagnosed between two study visits that were more than two years apart because of the increased uncertainty about their risk factor status at the time the cancer was diagnosed. We also excluded participants whose Surveillance, Epidemiology, and End Results program (SEER) Site ICD-0-3 cancer code was an epithelial-cell skin cancer (such as squamous cell carcinoma and basal cell carcinoma) because these cancers are not ascertained by the state cancer registries. Finally, cancers that were diagnosed within 24 hours of death were excluded because they represent a very different group of patients than those who were healthy enough to have the opportunity to receive treatment.

2.3 Primary Outcome Measures

The primary outcome of interest was all-cause mortality. Participant deaths were ascertained through medical record abstraction, National Death Index (NDI) matching, and by notification of family/next of kin. While causes of death were ascertained via NDI matching and from death certificates, we did not incorporate cause of death information into this study.

2.4 Primary Exposure Measures

Our primary objective was to evaluate the effect of HAART on cancer survival. As a means of achieving this, the primary exposures of interest were HAART era / HAART availability and HIV infection. We used calendar time as a metric to evaluate

the effectiveness of HAART. Calendar time was stratified into the pre-HAART and HAART eras. Patients with a cancer diagnosis prior to January 1, 1995 were classified as pre-HAART era patients, and patients with a cancer diagnosis after January 1, 1995 were classified as HAART era patients. HIV seropositivity was determined using blood drawn at each biannual visit. For MACS participants, enzyme-linked immunoadsorbent assays (EIA) were used to detect HIV seropositvity, and Western blot assays were used for confirmation (48). For WIHS participants, ultrafrozen sera samples were tested using the NASBA commercial assay to quantify HIV RNA viral load (49). HAART use in both cohorts in this study was defined based on the 2008 DHHS/Kaiser definitions. As of November 2008, HAART use in the MACS was defined as:

> "…three or more antiretroviral drugs consisting of one or more PIs or one NNRTI or the NRTIs - Abacavir or Tenofovir, or an integrase or an entry inhibitor. The percentages are based on total HIV+ person-visits with available therapy data from July 1995 to March 2010. …[s]pecific combinations subject to the following restriction criteria include (a) two or more NRTIs with one NNRTI or with one or more PIs (87%); (b)one NNRTI co-administered with one ritonavir (RTV) boosted PI with or without NRTI (7%); (c) an abacavir or tenofovir containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs (4%), (d) two or more RTV boosted PIs with or without other ARTs (1%); and (e) an integrase or entry inhibitor with a combination of two other antiretroviral drugs (1%) except for two unboosted PIs. Regimens containing the following combinations are not considered HAART: two or more NNRTIs, an NNRTI without a (RTV) boosted PI, unboosted atazanavir with TDF, boosted nelfinavir (NFV), and two NRTI combinations - zidovudine (AZT) + stavudine (d4T) or emtricitabine (FTC) + lamivudine (3TC). Enfuvirtide (T-20) or Maraviroc (Selzentry) or Ralegravir (Isenress) with two or more antiretroviral drugs except for all exclusions listed above were considered HAART. All other ART regimens were classified as combination therapy that did not meet the HAART definition" (53).

After April 2008, HAART use in the WIHS was defined as:

> "…the reported use of three or more antiretroviral medications, one of which has to be a PI, an NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor (e.g., raltegravir), or an entry inhibitor (e.g.,

Maraviroc or enfuvirtide)" (54).

2.5 Statistical Methods

For this analysis, since pre-HAART era data in the WIHS are limited, we utilized MACS data to compare cancer survival during the pre-HAART and HAART eras (Aim 1), and then used data from both WIHS and MACS accrued in the HAART era to determine whether cancer survival differs by HIV status or among HIV-infected participants who were taking HAART versus not taking HAART at the time of cancer diagnosis (Aim 2). For MACS participants who were diagnosed in the pre-HAART era, survival was censored at January 1, 1995 to prevent potential later HAART use from biasing the survival estimates of those whose cancers were diagnosed in the pre-HAART era. Additionally, the few cancers diagnosed among WIHS participants during the pre-HAART era were excluded. To account for different mechanisms of cancer development, we stratified cancers in two ways: (1) ADMs and non-ADMs, and (2) cancers that have been linked to a viral infection, and cancers that have not been linked to a viral infection. For this study, we classified anal, liver, stomach, vaginal, vulvar, oral, HL, KS (in HIV-uninfected individuals), NHL (in HIV-uninfected individuals), and cervical cancer (in HIV-uninfected individuals) as infection-related NADMs. Although some investigators have examined the hypothesis that prostate cancer has a viral etiology, we chose not to classify prostate cancer as an infection-related cancer because, unlike the other cancers we classified as infection-related NADMs, no one infectious agent has been definitively linked to prostate cancer. Cancer confirmation was based on multiple sources of information including biopsy, autopsy, imaging, medical records, and/or matching to state cancer registries. As cancer staging data was very limited, it was not included in this

analysis.

Demographic and clinical characteristics were assessed at the time of the visit prior to cancer diagnosis (Table 1). These cofactors included: age (<30 years, 30-39 years, 40-49 years, 50-59 years, ≥ 60 years), race (White, Black, and Other), sex, body mass index (categorized according to CDC guidelines as: underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), and overweight/obese (>25.0 kg/m^2)), intravenous drug use (current/non-current), smoking history (current/non-current). HIV-related cofactors were also assessed at the visit prior to cancer diagnosis. These cofactors included HIV viral load (>10,000 cp/ml as compared to <10,000 cp/ml), nadir CD4 cell count (<200 cells/μl as compared to >200 cells/μl), and prior AIDS diagnosis. We implemented a last observation carried forward imputation method for participants who had no more than a two-year gap between their last visit and the date of cancer diagnosis but were missing a value of a covariate at the visit prior to cancer diagnosis. This strategy allowed for values up to two years prior to the date of cancer diagnoses to be substituted for the missing values. Afterward, we conducted a complete case analysis.

We evaluated 5-year survival following cancer diagnosis using Kaplan-Meier curves and adjusted Cox proportional hazards models where survival time was calculated from the date of cancer diagnosis to the earliest of death or the last follow-up (censoring) date. We chose to examine 5-year survival instead of overall survival since it is a common prognostic measure used in cancer statistics (such as those reported by SEER), and because there of concern that beyond the 5-years survival trends may be driven by small sample size in certain groups (Figure 2) (5).

We assessed the proportional hazard assumption visually using complementary log-

log regression plots, and used the global log rank test to compare survival curves. When there was concern that the proportional hazards assumption was violated, we evaluated the extent of the violation by fitting unadjusted Cox time-dependent Relative Hazards regression model of the main effects and an interaction term between the main effects. If the interaction between the main effects was statistically significant based on the Wald test, we ran additional univariable Cox time-dependent Relative Hazards regression models that were stratified by the other main effect. Since in all the models where the proportional hazards assumption appeared to be violated, the issue could be isolated to a single group being compared, the final adjusted Cox time-dependent Relative Hazards regression model included an interaction with time for that particular group to address the issue of non-proportionality.

For each hypothesis, we fit univariable and multivariable Cox proportional hazard models compared them using the Akaike information criterion (AIC). The multivariable Cox models were adjusted for the following time-fixed cofactors assessed at the last visit prior to cancer diagnosis: age, race, intravenous drug use (IDU), smoking history, sex/cohort, body mass index (BMI), HIV viral load, nadir CD4 cell count, and prior AIDS diagnosis. We explored several different strategies (adjustment for sex, running separate models stratified by sex, and allowing for the baseline hazard functions to differ by sex) to account for substantial differences between the cohorts with regards to several covariates (ex. age, BMI, race). As these strategies yielded similar results, and based on a comparison of the AIC values, the models that allowed for differing baseline hazards appeared to be preferable, these models were presented as the final models.

All reported *P* values are two-sided and were considered statistically significant if $p \leq$

0.05. All data analyses were conducted using Stata, version 13.0 (Stata Corporation, College Station, Texas, USA).

3. RESULTS

The baseline demographic, clinical, and laboratory characteristics of the study population are described in Table 1. The 911 participants who met the inclusion criteria described in *Section 2.2* contributed a total of 2697.2 person-years of follow-up. There were a few notable differences between WIHS and MACS participants. The WIHS participants were slightly older than the MACS participants at the time of cancer diagnosis (median age (IQR): 48.1 (41.1 – 53.8) years, 41.2 (35.1 – 50.1) years, respectively, $p < 0.001$). The WIHS participants more frequently identified as Black, non-Hispanic (60.0%), while the MACS participants more frequently identified as White, non-Hispanic (84.5%) ($p < 0.001$). The WIHS participants also had higher BMIs than did the MACS participants (median BMI (IQR): 26.6 (22.0 – 32.4) kg/m^2 and 23.1 (21.4 – 25.3) kg/m^2, respectively, $p < 0.001$). Of the WIHS participants, 61% reported being current smokers at the visit prior to cancer diagnosis, as compared to about 27% of the MACS participants ($p < 0.001$). Among the smokers, the MACS participants had greater cumulative pack-years than did the WIHS participants (median cumulative pack-years (IQR): 24.0 (10.3 – 38.8) versus 14.9 (9.0 – 28.4), however, this difference was not statistically significant ($p = 0.10$). HIV-infection was more common among the WIHS participants than among the MACS participants (85.8% relative to 80.8%), and the WIHS participants were also more likely to have AIDS (51.0% relative to 17.7%, $p < 0.001$). Viral load was significantly higher among the MACS participants as compared to the WIHS participants (median viral load (IQR): 172,341 cp/ml (71,256 – 361,153 cp/ml) versus 23,000 cp/ml (4,300 – 110,000 cp/ml)), $p < 0.001$. Correspondingly, nadir CD4 cell count was also higher in the WIHS participants than did the MACS participants

(median CD4 cell count (IQR): 173 cells/μl (84 – 287 cells/μl) as compared to 106 cells/μl (42 – 247 cells/μl), $p < 0.001$).

The majority of incident cancers observed in the study population were ADMs (55.8%), followed by non-infection related NADMs (32.2%), and lastly infection-related ADMs (9.7%) (Table 2). As the MACS data included follow-up during both pre-HAART and HAART eras, and the WIHS follow-up was strictly from the HAART era, the majority of the ADMs were observed in MACS participants (91.5%). The three most common NADMs observed in the study population were: prostate cancer (14.2%), lung cancer (13.6%), and breast cancer (10.8%).

Aim 1: Hypothesis 1

We compared 5-year cancer survival during the pre-HAART and HAART eras among the 701 MACS participants who met the study inclusion criteria. During the 1460.3 person-years of follow-up the men accrued, 437 participants (62.3%) died within 5 years, yielding a 5-year mortality rate of 29.9 deaths / 100 person-years (95% CI: 27.2 – 32.9 deaths / 100 person-years). The 5-year mortality rates following cancer diagnosis by HIV status and era were: 4.7 deaths/100 person-years (95% CI: 2.6 – 7.9) for HIV(-) participants diagnosed in the HAART era, 16.3 deaths/100 person-years (95% CI: 9.8 – 25.4) for HIV(-) participants diagnosed in the pre-HAART era HIV(-), 12.2 deaths/100 person-years (95% CI: 9.2 – 15.9) for HIV(+) participants diagnosed in the HAART era, 58.6 deaths/100 person-years (95% CI: 52.6 – 65.1) for HIV(+) participants diagnosed in the pre-HAART era.

The Kaplan-Meier curves for participants by HIV status and era showed that the 5-year cumulative probability of survival following a cancer diagnosis was lowest among

HIV(+) participants diagnosed with cancer the in pre-HAART era (0.06, 95% CI: 0.04 – 0.10) and highest among HIV(-) participants diagnosed in the HAART era (0.81, 95% CI: 0.70 – 0.88) (Figure 3). The global log rank test indicated that the survival curves were statistically significantly different ($p < 0.001$). The curves for HIV(-) participants in the pre-HAART era and HIV(+) participants in the HAART era were roughly equivalent. Visual inspection of the complementary log-log regression plot comparing the four groups indicated that the proportional hazards assumption was violated. To determine the extent of the violation of the proportional hazards assumption, we fit univariable Cox time-dependent Relative Hazards regression models of the main effects (HIV status and era). As only the interaction between era and time was statistically significant based on the Wald test ($p = 0.001$), additional univariable Cox time-dependent Relative Hazards regression models of era were run separately for HIV(+) and HIV(-) participants. The interaction between era and time was only significant for the HIV(+) participants ($p < 0.001$), and so the final multivariable Cox time-dependent Relative Hazards regression model included an interaction with time for HIV(+) participants in the pre-HAART era (Table 4).

In the final adjusted model examining the cancer survival by HIV status and HAART era, the interaction term between time and HIV(+) participants who received a cancer diagnosis in the pre-HAART era was statistically significant, which indicated that the relative hazard increased with time (adjusted hazard ratio, 1.70 per year; 95% CI, 1.39 – 2.07). Based on this model, the adjusted relative hazard 2 years after cancer diagnosis increased to 2.81 (95% CI, 1.35 – 5.83) and then to 8.08 (95% CI, 3.36 – 19.42) after 4 years. Participants who were diagnosed after age 60 years had a lower hazard of death as

compared to participants diagnosed before age 30 years. Participants who were overweight or obese at the last visit prior to cancer diagnosis had a lower hazard of death relative to normal weight participants, while those with a prior AIDS diagnosis had a greater hazard of death relative those without an AIDS diagnosis. Among HIV(+) participants, viral load > 10,000 cp/ml and nadir CD4 cell count < 200 cells/μl were each significantly associated with a higher hazard of death.

Aim 1: Hypothesis 2

To explore the impact of the introduction of HAART on cancer survival further, we next examined cancer survival among individuals diagnosed with ADMs and NADMs. In the 5-year analysis, 556 MACS participants who were HIV(+) at the visit prior to cancer diagnosis, met the inclusion/exclusion criteria described above, and did not have a "Miscellaneous" SEER code contributed a total 1,021.6 person-years of follow-up. Among these participants, 397 participants (71.4%) participants died during follow-up, yielding a 5-year mortality rate of 38.9 deaths/100 person-years (95% CI: 35.1 – 42.9).

We first explored differences in cancer survival by cancer type (ADM vs. NADM) and era. The 5-year mortality rates by era and cancer type were: 6.5 deaths/100 person-years (95% CI: 3.7 – 10.6) among participants diagnosed with NADMs in the HAART Era, 18.5 deaths/100 person-years (95% CI: 12.9 – 25.7) among participants diagnosed with ADMs in the HAART era, 27.1 deaths/100 person-years (95% CI: 13.5 – 48.5) among participants diagnosed with NADMs in the pre-HAART era, and 61.4 deaths/100 person-years (95% CI: 55.0 – 68.4) among participants diagnosed with ADMs in the pre-HAART era. The Kaplan-Meier curves comparing survival of participants

diagnosed with an NADM in the HAART Era, participants diagnosed with an ADM in the HAART era, participants diagnosed with an NADM in the pre-HAART era, and participants diagnosed with an ADM in the pre-HAART era suggested that the 5-year hazard of death following a cancer diagnosis was highest among participants diagnosed with an ADM in the pre-HAART era and lowest among participants diagnosed with an NADM in the HAART era (Figure 4). The global log rank test indicated that the curves were significantly different ($p < 0.001$) The curves of participants diagnosed with an ADM in the HAART era and participants diagnosed with an NADM in the pre-HAART were fairly similar, with participants diagnosed with ADMs in the HAART era appearing to have slightly improved survival after one year of follow-up. Visual inspection of the complementary log-log regression plot comparing the four groups indicated that the proportional hazards assumption was violated. The extent of the violation of the proportional hazards assumption was assessed as described previously. Based on the results, the final adjusted Cox time-dependent Relative Hazards regression model included an interaction with time for participants diagnosed with ADMs in the pre-HAART era (Table 6).

In this final adjusted model, the interaction term between time and HIV(+) participants who received a cancer diagnosis in the pre-HAART era was statistically significant, which indicates that the relative hazard increased over time (adjusted HR increase per year, 1.74; 95% CI: 1.39 – 2.19). Based on this model, the adjusted relative hazard 2 years after cancer diagnosis increased to 7.68 (95% CI, 3.89 – 15.18) and then to 23.2 (95% CI, 9.41 – 57.3) after 4 years. As the Kaplan-Meier curves indicated, individuals diagnosed with ADMs in the pre-HAART era had the greatest hazard of

death, followed by participants diagnosed with NADMs in the pre-HAART era (adjusted HR: 4.91; 95% CI: 2.12 – 11.39), and then participants diagnosed with ADMs in the HAART era (adjusted HR: 2.12; 95% CI: 1.08 – 4.50). Participants who were overweight or obese at the visit prior to cancer diagnosis had a lower hazard of death relative to normal weight participants. Having a prior AIDS diagnosis, being a current smoker, having a viral load > 10,000 cp/ml, and having a nadir CD4 cell count < 200 cells/μl were each associated with a greater hazard of death.

Aim 1: Hypothesis 3

Next, we explored cancer survival by cancer type (infection-related or non-infection related) and era using the same 556 MACS participants described in *Aim 1: Hypothesis 2*. The 5-year mortality rates by era and cancer type were as follows: 4.6 deaths/100 person-years (95% CI: 1.8 – 9.4) among participants diagnosed with non-infection-related cancers in the HAART era, 15.6 deaths/100 person-years (95% CI: 11.3 – 20.9) among participants diagnosed with infection-related cancers in the HAART era, 37.1 deaths/100 person-years (95% CI: 17.0 – 70.4) among participants diagnosed with non-infection-related cancers in the pre-HAART era, and 60.0 deaths/100 person-years (95% CI: 53.8 – 66.8) among participants diagnosed with infection-related cancers in the pre-HAART era.

The Kaplan-Meier curves comparing survival of participants cancer type (infection-related or non-infection related) and era indicated that the 5-year hazard of death following a cancer diagnosis was highest among participants diagnosed with infection-related cancers in the pre-HAART era and lowest among participants diagnosed with non-infection-related cancers in the HAART era (Figure 5). During the first 18

months of follow-up, the curves for participants diagnosed with infection-related cancers in the HAART era, participants diagnosed with non-infection related cancers in the pre-HAART era, and participants diagnosed infection-related cancers in the pre-HAART era intersected several times, but thereafter, survival was better among participants diagnosed with infection-related cancer in the HAART era, followed by participants diagnosed with non-infection related cancers in the pre-HAART era, and then participants diagnosed with infection-related cancers in the pre-HAART era. The global log rank test indicated that the survival curves were statistically different ($p < 0.001$). Visual inspection of the complementary log-log regression plot comparing the four indicated that the proportional hazards assumption was violated. The extent of the violation of the proportional hazards assumption was assessed as described previously. Based on the results, the final adjusted Cox time-dependent Relative Hazards regression model included an interaction with time for participants diagnosed with infection-related cancers in the pre-HAART era (Table 7).

In this final adjusted model, individuals diagnosed with non-infection-related cancers in the pre-HAART era had a 6.56 times greater hazard of death relative to those diagnosed with non-infection related cancers in the HAART era (95% CI: 2.33 – 18.48). Once the interaction term between time and participants diagnosed with infection-related cancers who received a cancer diagnosis in the pre-HAART era was included in the model, the effect for participants diagnosed with infection-related cancers in the pre-HAART era was no longer significant ($p = 0.06$), however, the interaction term was. This indicated that the relative hazard increases in a log-linear fashion (adjusted HR increase per year, 1.72; 95% CI: 1.36 – 2.18). Based on this model, the adjusted relative hazard 2 years after cancer diagnosis increased to 7.33 (95% CI: 3.02 – 17.84) and then to 21.71

(95% CI: 7.38 – 63.82) after 4 years. Participants who were overweight or obese at the last visit prior to cancer diagnosis had a lower hazard of death relative to normal weight participants. Being a current smoker, having a prior AIDS diagnosis, and having a nadir CD4 cell count < 200 cells/μl, were each independently associated with significantly greater hazards of death.

Aim 2: Hypothesis 1

In Aim 2, we explored the effect of HAART on cancer survival more directly by comparing survival between those taking versus not taking HAART immediately prior to cancer diagnosis. Subsequent analyses were restricted to the HAART era and included participants from both MACS and WIHS cohorts. In the 5-year survival analysis, the 439 participants who met the inclusion/exclusion criteria described in *Section 2.2* contributed a total of 1257.2 person years of follow-up. Among these participants, 229 participants (52.2%) died during follow-up, and the 5-year mortality rate was 18.2 deaths/100 person-years (95% CI: 15.9 – 20.7). The cohort-specific 5-year mortality rates were: 31.4 deaths/100 person-years (95% CI: 26.7 – 36.7) for WIHS and 9.2 deaths/100 person-years (95% CI: 7.2 – 11.7). The 5-year mortality rates following cancer diagnosis by HIV status and HAART use were as follows: 8.9 deaths/100 person-years (95% CI: 6.2 – 12.4) for HIV(-) participants, 19.7 deaths/100 person-years (95% CI: 16.1 – 24.0) for HIV(+) participants using HAART at the visit prior to cancer diagnosis, and 25.8 deaths/100 person-years (95% CI: 20.9 – 31.5) for HIV(+) participants not using HAART at the visit prior to cancer diagnosis.

The Kaplan-Meier curves comparing survival of participants by HIV status and HAART use suggested that the 5-year hazard of death following a cancer diagnosis was

highest among HIV(+) participants not using HAART and lowest among HIV(-) participant (Figure 6). The global log rank test results indicated that the survival curves were statistically different ($p < 0.001$). Visual inspection of the complementary log-log regression plot comparing the three indicated that the proportional hazards assumption was likely not violated. To confirm this, we assessed the potential for violation of the proportional hazards assumption as described previously. None of the stratified results indicated that there was a group whose description of the relative hazard would be improved by including an interaction with time, suggesting that the assumption was not violated.

The final adjusted model allowed for differing baseline hazards by cohort to account for aforementioned notable differences between the two cohorts (Table 9). In this model, HIV(+) participants using HAART had a lower hazard of death relative to HIV(-) participants, and HIV(+) not using HAART had a greater hazard of death relative to HIV(-) participants however, neither of these were statistically significant (adjusted HR: 0.92; 95% CI: 0.57 – 1.48; adjusted HR: 1.26; 95% CI: 0.78 – 2.05, respectively). HIV(+) participants not using HAART had a statically significant greater hazard of death than did those using HAART (adjusted HR: 1.38; $p = 0.05$). Individuals who were current smokers had a greater hazard of death relative to non-current smokers. Additionally, having a prior AIDS diagnosis and having a nadir CD4 cell count < 200 cells/μl were each associated with a greater hazard of death.

Aim 2: Hypothesis 2

Next, we explored cancer survival by cancer type (NADM or ADM, infection-related or non-infection related) and HAART use among HIV(+) individuals whose

cancer was not classified as "Miscellaneous." In the five-year survival analysis, the 310 participants who met the inclusion/exclusion criteria described in *Section 2.2* contributed a total of 847.0 person years of follow-up. Among these participants, 184 participants (59.3%) died during follow-up, and the 5-year mortality rate was 21.7 deaths/100 person-years (95% CI: 18.7 – 25.1). The 5-year mortality rates following cancer diagnosis by cancer type (NADM or ADM) and HAART use were: 19.1 deaths/100 person-years (95% CI: 15.0 – 23.9) for individuals diagnosed with NADMs using HAART, 18.6 deaths/100 person-years (95% CI: 11.0 – 29.4) for individuals diagnosed with ADMs and using HAART, 24.8 deaths/100 person-years (95% CI: 17.9 – 33.5) for individuals diagnosed with NADMs not using HAART, and 26.0 deaths/100 person-years (95% CI: 19.3 – 34.4) for individuals diagnosed with ADMs not using HAART.

The Kaplan-Meier curves comparing survival of participants by cancer type and HAART use indicated that the 5-year hazard of death following a cancer diagnosis was highest among individuals diagnosed with ADMs not using HAART and lowest among individuals diagnosed with NADMs using HAART (Figure 7), however, each of the survival curves intersected another at some point during the 5 year follow-up. The results of the global log rank test indicated that the survival curves were not different ($p = 0.24$). Visual inspection of the complementary log-log regression plot comparing the four groups suggested that the proportional hazards assumption was not violated.

The final adjusted model allowed for differing baseline hazards by cohort to account for aforementioned differences between the cohorts (Table 11). In this model, HIV(+) individuals using HAART had a lower hazard of death as compared to HIV(+) individuals not using HAART, and this effect was statistically significant (adjusted HR:

0.68; 95% CI: 0.48 – 0.96). An interaction term between cancer type and HAART use was included in one of the earlier models to test for effect modification, and as it was not significant ($p = 0.22$), it was not included in the final model. Individuals who identified as Black, non-Hispanic had a greater hazard of death as compared to individuals who identified as White, non-Hispanic. Furthermore, having a prior AIDS diagnosis and a nadir CD4 cell count < 200 cells/μl were also independently associated with an elevated hazard of death.

Aim 2: Hypothesis 3

Lastly, we evaluated cancer survival by cancer type (infection-related or non-infection-related) and HAART use using the same 310 participants described in *Aim 2: Hypothesis 2*. The 5-year mortality rates following cancer diagnosis by cancer type and HAART use were: 16.2 deaths/100 person-years (95% CI: 11.3 – 22.4) for individuals diagnosed with infection-related cancers using HAART, 21.3 deaths/100 person-years (95% CI: 16.2 – 27.7) for individuals diagnosed with non-infection-related cancers using HAART, 22.6 deaths/100 person-years (95% CI: 15.6 – 31.6) for individuals diagnosed with non-infection-related cancers not using HAART, and 27.5 deaths/100 person-years (95% CI: 20.9 – 35.7) for individuals diagnosed with infection-related cancers not using HAART.

The Kaplan-Meier curves comparing survival of participants by cancer type and HAART use indicated that the 5-year hazard of death following a cancer diagnosis was highest among individuals diagnosed with infection-related-cancers not using HAART and lowest among individuals diagnosed with infection-related cancers using HAART (Figure 8), however, the survival curves of participants other than those diagnosed with

infection-related cancers not using HAART were similar. The results of global the log rank test indicated that the survival curves for the four groups were not different (p = 0.10). Visual inspection of the complementary log-log regression plot comparing the four groups suggested that the proportional hazards assumption was not violated.

The final adjusted model allowed for differing baseline hazards by cohort to account for aforementioned differences between the two cohorts (Table 12). Based on this model, participants diagnosed with non-infection-related cancers using HAART at the visit prior to cancer diagnosis had 1.07 times the hazard of death as compared to those not using HAART, however, this elevated hazard was not significant (95% CI: 0.67 – 1.72). Individuals diagnosed with infection-related cancers using HAART had a statistically significant lower hazard of death as compared to those not using HAART (adjusted HR: 0.36, 95% CI: 0.19 – 0.69) (Table 13). This indicated that HAART improved survival for participants diagnosed with infection-related cancers but had little or no effect on survival for individuals diagnosed with non-infection-related cancers. The interaction term between the HAART use and infection-related cancer was statistically significant, which indicated that the effect of having an infection-related cancer was modified by HAART use (p = 0.002). Therefore, according to this model, among HAART non-users, HIV(+) participants diagnosed with infection-related cancers had 1.98 times the hazard of death as compared to HIV(+) participants diagnosed with non-infection-related cancers (95% CI: 1.18 – 3.32). Among HAART users, HIV(+) participants diagnosed with infection-related cancers had 0.71 times the hazard of death as compared to HIV(+) participants diagnosed with non-infection related cancers (95% CI: 0.44 – 1.13). Participants who identified as Black, non-Hispanic had a greater hazard

of death relative to individuals who identified as White, non-Hispanic. Having a prior AIDS diagnosis and a nadir CD4 cell count < 200 cells/μl were each independently associated with a greater hazard of death.

4. DISCUSSION

Since the start of the AIDS pandemic, cancer has been an important cause of mortality among individuals living with HIV. This study examines the impact of HAART in two ways – by comparing mortality in the pre-HAART and HAART eras and also by comparing mortality during the HAART era between those where taking versus not taking HAART at the time cancer was diagnosed. Our finding of the improved survival among HIV-infected individuals with cancers diagnosed in the HAART era compared to those diagnosed in the pre-HAART era is consistent with previous studies (34,35). During the HAART era, we found that cancer survival was statistically indistinguishable between HIV-infected and HIV-uninfected individuals nor did survival differ among HIV-infected individuals diagnosed with ADMs as compared to those diagnosed with NADMs. Interestingly, we observed that cancer survival differed significantly by HAART use among those diagnosed with infection-related cancers, but not among those diagnosed with non-infection-related cancers. Taken together, the results from this study demonstrate the important role of HAART in cancer survival for individuals diagnosed with infection-related cancers and support the need for future research into how the impact of HAART varies by cancer type among individuals with infection-related cancers.

In our analysis comparing cancer survival among all study participants diagnosed with cancer in the pre-HAART and the HAART eras, we found that HIV-infected individuals with cancers diagnosed in the HAART era had improved survival compared to those diagnosed in the pre-HAART era. This finding is consistent with those reported in previous studies (34,35). Among HIV-infected individuals, we noted that participants diagnosed with NADMs in the pre-HAART era had a greater hazard of death as

compared to participants diagnosed with NADMs in the HAART era, and that participants diagnosed with ADMs in the HAART era had a greater hazard of death than did individuals diagnosed with NADMs in the HAART era. We also examined survival in the pre-HAART and HAART eras among HIV-infected individuals for infection-related versus non-infection-related cancers, and found that the cancer survival increase following the introduction of HAART was greater for participants diagnosed with infection-related cancers. Participants with infection-related cancers diagnosed in the pre-HAART era had an elevated hazard of death at baseline that increased by a factor of 1.72 per year following cancer diagnosis, relative to individuals diagnosed in the HAART era. In comparison, participants diagnosed with non-infection-related cancers in the pre-HAART era had 6.56 times the hazard of death relative to individuals diagnosed in the HAART era. Although, the greater improvement in survival among individuals diagnosed with infection-related cancers was anticipated given that HAART improves immune function, previous studies have demonstrated that the relationship between HAART and HIV infection is complicated and the timing of HAART initiation has been shown to be instrumental (44–46).

Comparing survival by HIV status in the HAART era in Aim 1, without accounting for HAART use, we noted that survival was comparable among HIV-infected and HIV-infected participants. When included HAART use information in Aim 2, we again saw no statistically significant difference in the hazard of death of HIV-uninfected as compared to HIV-infected individuals both using and not using HAART. Previous studies, on the other hand, have reported that, perhaps with the exception of NHL, there remains a gap in survival between HIV-infected and HIV-uninfected individuals in the

HAART era (36,38). The main contributor to improved survival among HIV-infected individuals is undoubtedly HAART use, as mortality was higher among HIV-infected participants not using HAART in the HAART era relative to those using HAART. Together with our finding that survival among HIV-uninfected individuals did not differ significantly in the two eras, this suggests that the improved survival for HIV-infected individuals in the HAART era is not primarily due to advances in cancer treatment over time or other secular trends not specific to HIV-infected individuals. Rather, it is most likely to be attributed to HAART use as well as possibly to improvements in clinical surveillance improved for HIV-infected individuals, particularly those with risk factors for cancer, as the lifespan of individuals living with HIV increased and they began developing aging-related conditions.

Examining the impact of HAART use on survival in the HAART era, we observed that there was no difference in survival by cancer type (ADM vs. NADM), but that individuals taking HAART at the visit prior to cancer diagnosis had a significantly lower hazard of death than those not taking HAART. This result is consistent with several previous studies that reported that survival does not differ for HIV-infected individuals diagnosed with ADMs as compared to those diagnosed with NADMs (34,40). One study, however, reported that HAART is less effective for individuals diagnosed with NADMs than for individuals diagnosed with ADMs (41).

Interestingly, when we examined the impact of HAART on survival by cancer type (infection-related versus not infection-related), we found that HAART only appears to have an impact for individuals diagnosed with infection-related cancers. Specifically, the interaction term between infection-related cancer and HAART use was highly

significant, but the effect of HAART for those with non-infection-related cancers was not significant. Stratified by HAART use, non-HAART using HIV(+) participants diagnosed with infection-related cancers a greater the hazard of death as compared to HIV(+) participants diagnosed with non-infection-related cancers. Among HAART users, however, HIV(+) participants diagnosed with infection-related cancers had decreased hazard of death as compared to HIV(+) participants diagnosed with non-infection related cancers. Since HAART improves immune function, it was anticipated that it would also improve control of co-infections, and thereby lead to improved survival among co-infected individuals. Our results are consistent with those from a multicenter prospective study, which reported that individuals diagnosed with ADMs and infection-related NADMs, both had a lower hazard of death relative to individuals diagnosed with infection-unrelated NADMs (46).

This study has important strengths and limitations. A key strength of this study was the recruitment of HIV-uninfected participants in addition to HIV-infected participants, which provided an internal comparison group. The presence of an internal comparison group enabled us to obtain more accurate estimates of the hazard of death than could be calculated using an external comparison group (such as that from the general population). Another important strength is that we possessed both pre-HAART era and HAART era data. This allowed us to compare survival before and after the introduction of HAART and to examine HAART use in two ways – using HAART era as a proxy for HAART use and using actual HAART use data for individuals diagnosed in the HAART era.

A number of limitations should be considered. We could not include cancer stage/grade data in this analysis since it was limited, however, this data is an important predictor of hazard of death, and our hazard ratio estimates would be improved by its inclusion. The estimates could also be improved by the inclusion of income (or another predictor of socioeconomic status such as employment) and education as covariates. Additionally, we did not examine cause of death in our analysis, and as such did not investigate the possibility that survival differences could be due to differential cancer-specific mortality rates. Another limitation is that this analysis included time-fixed covariates assessed at the visit prior to cancer diagnosis, and as such did not allow for individuals to switch exposure groups during the course of the analysis. Finally, we did not account for lack of adherence to HAART treatment. Future analyses will be performed to extend the current analysis by addressing these limitations where possible.

In conclusion, although HAART has dramatically extended the lifespan and improved the quality of life of individuals living with HIV, it has also resulted in an increase in aging-related morbidities among those infected with HIV. Certain NADMs in the HIV-infected population are on the rise, and there is a need to work towards improving cancer prevention and treatment in this population (23,24). The findings of this study demonstrate that HAART use is associated with a lower hazard of death for individuals diagnosed with infection-related cancers. Future research should extend the current study by examining the impact of HAART on survival among those diagnosed with infection-related cancers varies by cancer type to determine whether the beneficial effect is related to systemic immunocompetence or if it might be etiologically related to specific cancers.

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of Study Participants

Characteristic	Total (*n* = 911)			WIHS (*n* = 210)			MACS (*n* = 701)			p-value[a]
	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	
Age (in years)	42.5 (36.2 – 51.5)			48.1 (41.1 – 53.8)			41.2 (35.1 – 50.1)			
< 30		49	5.4		5	2.4		44	6.3	
30 - 39		302	33.2		39	18.6		263	37.5	
40 - 49		301	33.0		84	40.0		217	31.0	
50 - 59		178	19.5		65	31.0		113	16.1	
60 +		81	8.9		17	8.1		64	9.1	**<0.001**
Race										
White, non-Hispanic		627	68.8		35	16.7		592	84.5	
Black, non-Hispanic		189	20.7		126	60.0		63	9.0	
Other		95	10.4		49	23.3		46	6.6	**<0.001**
IDU										
Never		724	79.5		121	57.6		603	86.0	
Former		168	18.4		82	39.1		86	12.3	
Current		19	2.1		7	3.3		12	1.7	**<0.001**
BMI	23.5 (21.4 – 26.3)			26.6 (22.0 – 32.4)			23.1 (21.4 – 25.3)			
Normal (18.5 – 24.9)		552	60.6		68	32.4		484	69.0	
Underweight (< 18.5)		39	4.3		19	9.0		20	2.9	
Overweight (25.0 – 29.9)		206	22.6		48	22.9		158	22.5	
Obese (30 +)		114	12.5		75	35.7		39	5.6	**<0.001**
Smoking History										
Never		255	28.0		29	13.8		226	32.2	
Former		339	37.2		53	25.2		286	40.8	
Current		317	34.8		128	61.0		189	27.0	**<0.001**

Abbreviations: IDU, Intravenous Drug User; BMI, Body Mass Index (Weight (kg) / Height (m^2))

[a]Pearson's χ^2 was used for categorical variables. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables.

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of Study Participants (continued)

Characteristic	Total (*n* = 911)			WIHS (*n* = 210)			MACS (*n* = 701)			p-value[a]
	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	
Year of Cancer Diagnosis										
1984 - 1994		472	51.8		N/A	0.0		472	67.3	
1995 - 2013		439	48.2		210	100.0		229	32.7	**<0.001**
HIV/AIDS Status										
HIV -		165	18.1		30	14.3		135	19.3	
HIV + / AIDS -		515	56.5		73	34.8		442	63.1	
HIV + / AIDS +		231	25.4		107	51.0		124	17.7	**<0.001**
HIV Viral Load (among HIV+)	141,988 (43,000 – 330,000)			23,000 (4,300 – 110,000)			172,341 (71,256 – 361,153)			
Undetectable (< 400 cp/ml)		140	18.8		71	39.4		69	12.2	
< 10,000 cp/ml		77	10.3		39	21.7		38	6.7	
> 10,000 cp/ml		529	70.9		70	38.9		459	81.1	**<0.001**
Nadir CD4 Cell Count (among HIV+)	123 (45 – 262)			173 (84 – 287)			106 (42 – 247)			
> 200 cells/µl		251	33.7		80	44.4		171	30.2	
< 200 cells/µl		495	66.4		100	55.6		395	69.8	**<0.001**
HAART Experienced (among HIV+)										
No		562	75.3		78	43.3		484	85.5	
Yes		184	24.7		102	56.7		82	14.5	**<0.001**

Abbreviations: HAART, Highly Active Antiretroviral Therapy

[a]Pearson's χ^2 was used for categorical variables. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables.

Table 2. Numbers of Cancers by Cancer Type Among Study Participants

Cancer Type	Total (*n* = 911)		WIHS (*n* = 210)		MACS (*n* = 701)	
	No.	**%**	**No.**	**%**	**No.**	**%**
ADM	**508**	**55.8**	**43**	**20.5**	**465**	**66.3**
NHL	124		32		92	
KS	380		7		373	
ICC	4		4		N/A	
NADM - Infection-related	**88**	**9.7**	**25**	**11.9**	**63**	**9.0**
Anal	25		4		21	
Liver	12		3		9	
Stomach	3		2		1	
Vaginal	1		1		N/A	
Vulvar	2		2		N/A	
Oral Cavity and Pharynx	13		6		7	
Hodgkin's Lymphoma	12		5		7	
NHL, HIV(-)	10		2		8	
KS, HIV(-)	10		0		10	
NADM - Non-Infection-related	**293**	**32.2**	**132**	**62.9**	**161**	**23.0**
Colon	16		7		9	
Rectum	11		2		9	
Pancreas	5		3		2	
Lung	52		38		14	
Bones/Joints	1		0		1	
Soft Tissue incl. heart	4		2		2	
Melanoma	29		4		25	
Other Non-Epithelial Skin Cancer	2		0		2	
Breast	41		41		N/A	
Uterus	6		6		N/A	
Ovary	1		1		N/A	
Prostate	54		N/A		54	
Testis	4		N/A		4	
Urinary Bladder	7		1		6	
Kidney and Renal Pelvis	7		3		4	
Brain/CNS	7		4		3	
Thyroid/Pituitary	5		3		2	
Myeloma	10		3		7	
Leukemia	11		4		7	
Nose, Nasal Cavity, and Middle Ear	2		0		2	
Other Endocrine incl. thymus	2		0		2	
Esophagus	2		0		2	
Larynx	9		7		2	
Ureter	1		0		1	
Small Intestine	2		1		1	
Gallbladder	2		2		0	
Misc.	**22**	**2.4**	**10**	**4.8**	**12**	**1.7**

Abbreviations: ADM, AIDS-Defining Malignancy; NADM, Non-AIDS-Defining Malignancy

Figure 1. Inclusion/Exclusion Flowchart for the MACS and WIHS Participants

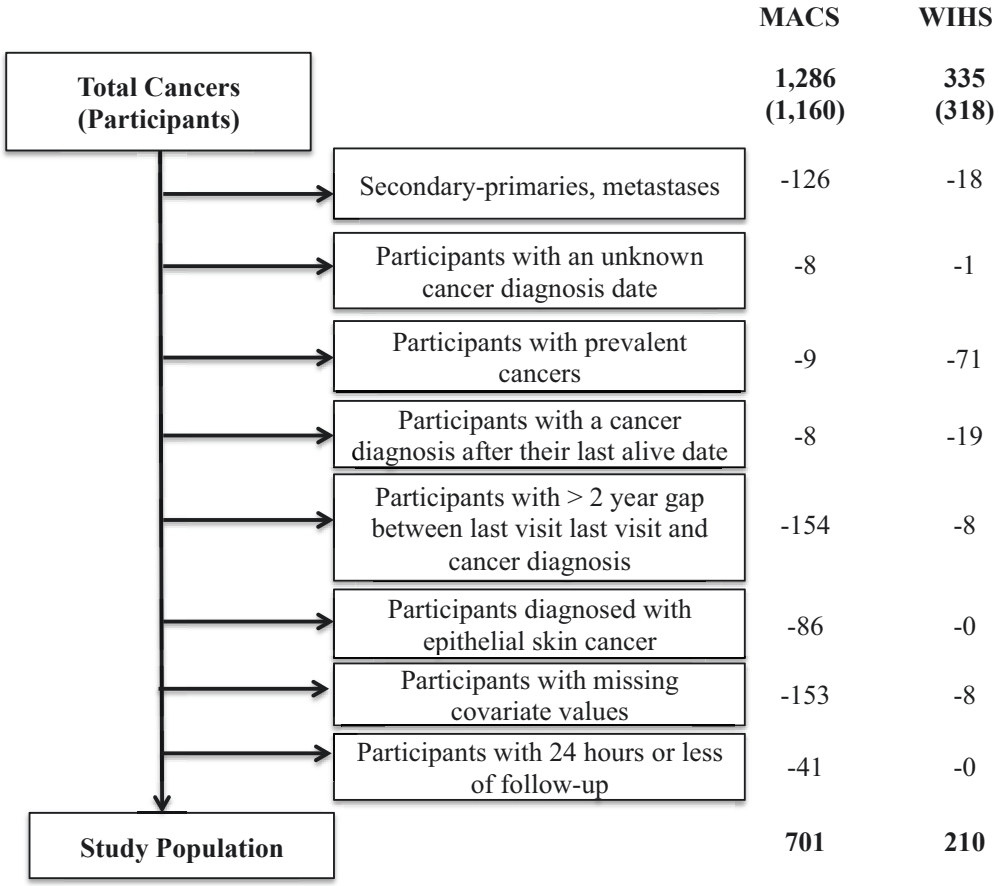
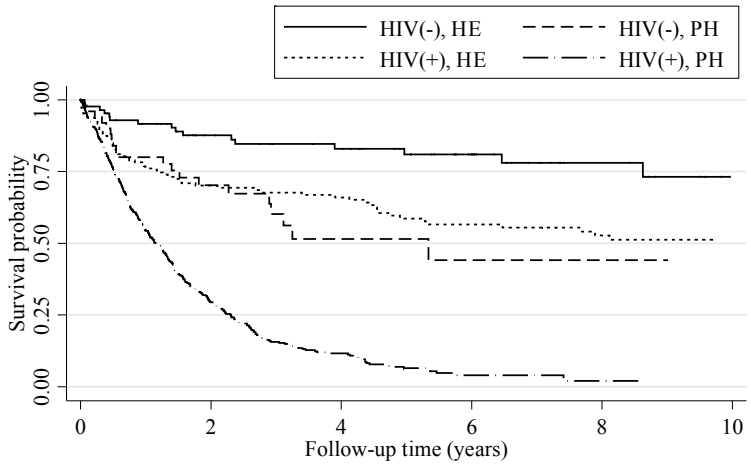


Figure 2. 10-Year Unadjusted Cancer Survival Plot by HAART Era and HIV Status in the MACS

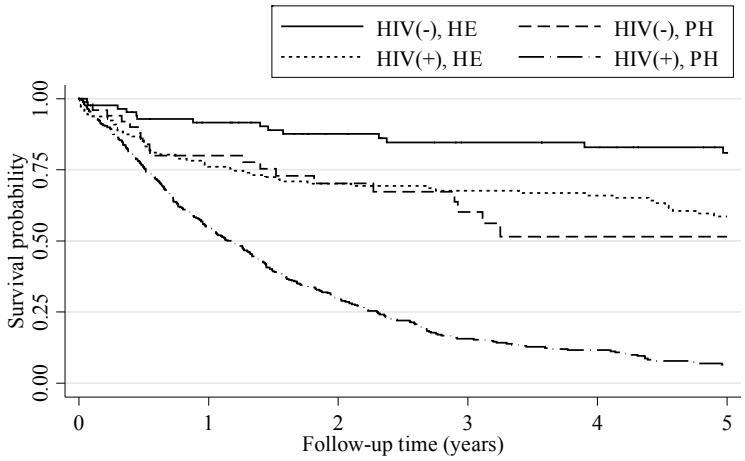


Number at risk						
HIV(-), HE	85	59	49	33	17	8
HIV(-), PH	50	24	10	5	2	0
HIV(+), HE	144	89	77	52	38	30
HIV(+), PH	422	104	28	5	1	0

Abbreviations: HE, HAART Era; PH, pre-HAART Era

Figure 3. A) 5-Year Unadjusted Cancer Survival Plot by HAART Era and HIV Status in the MACS, B) Plot of the Relative Hazard as a Function of Time Comparing Survival for HIV+ participants diagnosed with cancer in the pre-HAART Era (HIV+, PH) relative to HIV- participants diagnosed with cancer in the HAART Era (HIV-, HE)

A)



Number at risk						
HIV(-), HE	85	73	59	52	49	42
HIV(-), PH	50	37	24	16	10	7
HIV(+), HE	144	107	89	81	77	58
HIV(+), PH	422	218	104	43	28	13

Abbreviations: HE, HAART Era; PH, pre-HAART Era

B)

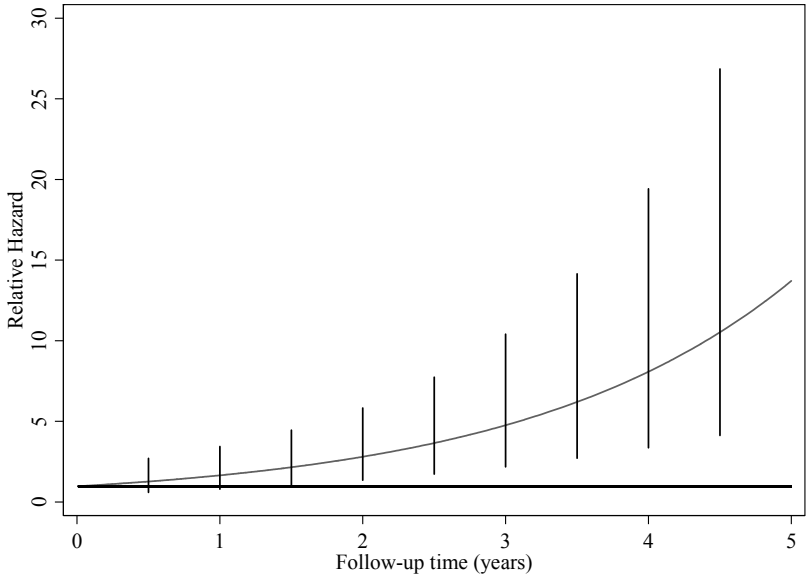


Table 3. Univariable Cox Proportional Hazards Models of Mortality Comparing Cancer Survival Among HIV-infected and –uninfected Individuals Diagnosed with Cancer in the pre-HAART (1984-1994) and the HAART (1995-2013) Eras

	HR	95% CI	p-value[a]
HIV Infection			
No	REF		
Yes	4.35	3.05, 6.21	**<0.001**
Era			
Pre-HAART	REF		
HAART	0.21	0.16, 0.27	**<0.001**
Age (years)			
< 30	1.18	0.95, 1.46	0.13
30 - 39	1.76	1.24, 2.49	**0.001**
40 - 49	REF		
50 - 59	0.39	0.27, 0.55	**<0.001**
60 +	0.12	0.06, 0.25	**<0.001**
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	0.68	0.47, 0.98	**0.04**
Other	1.42	1.01, 2.01	**0.04**
IDU			
Never/Former	REF		
Current	1.09	0.52, 2.30	0.82
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.57	0.95, 2.59	0.08
Overweight/Obese (25.0 +)	0.44	0.34, 0.56	**<0.001**
Smoking History			
Never/Former	REF		
Current	1.28	1.04, 1.57	**0.02**
Prior AIDS Diagnosis			
No	REF		
Yes	2.69	2.15, 3.36	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	5.10	3.91, 6.64	**<0.001**
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	3.37	2.72, 4.17	**<0.001**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

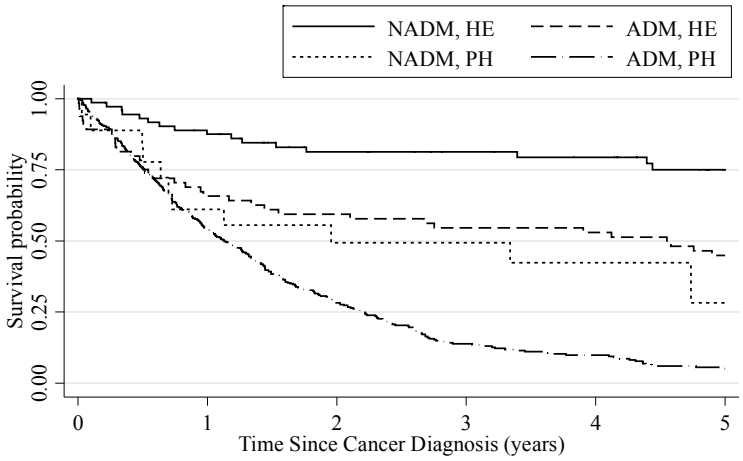
Table 4. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival Among HIV-infected and –uninfected Individuals Diagnosed with Cancer in the pre-HAART (1984-1994) and the HAART (1995-2013) Eras

	HR	95% CI	p-value[a]
HIV Status and Era			
HIV(-), HAART Era	REF		
HIV(-), pre-HAART Era	1.94	0.93, 4.05	0.08
HIV(+), HAART Era	0.70	0.35, 1.38	0.30
HIV(+), pre-HAART Era	0.97	0.44, 2.15	0.95
Interaction with time for HIV(+), pre-HAART Era	1.70	1.39, 2.07	**<0.001**
Age (years)			
< 30	REF		
30 - 39	0.77	0.54, 1.08	0.13
40 - 49	0.87	0.61, 1.24	0.45
50 - 59	0.71	0.43, 1.17	0.18
60 +	0.39	0.16, 0.91	**0.03**
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	0.96	0.65, 1.42	0.84
Other	1.24	0.87, 1.75	0.23
IDU			
Never/Former	REF		
Current	1.00	0.46, 2.15	1.00
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.41	0.85, 2.36	0.18
Overweight/Obese (25.0 +)	0.76	0.59, 0.98	**0.03**
Smoking History			
Never/Former	REF		
Current	1.40	1.13, 1.73	**0.002**
Prior AIDS Diagnosis			
No	REF		
Yes	1.89	1.49, 2.41	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.58	1.03, 2.41	**0.04**
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	2.29	1.76, 2.99	**<0.001**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

Figure 4. 5-Year Unadjusted Cancer Survival Plot by HAART Era and Cancer Type Among HIV-infected participants in the MACS, B) Plot of the Relative Hazard as a Function of Time Comparing Survival for Participants Diagnosed with ADMs in the pre-HAART Era (ADM, PH) relative to Participants Diagnosed with NADMs in the HAART Era (NADM, HE)

A)



Number at risk						
NADM, HE	73	62	49	44	41	28
ADM, HE	65	42	37	34	33	28
NADM, PH	18	11	8	7	4	2
ADM, PH	400	204	94	35	23	10

Abbreviations: NADM, Non-AIDS-Defining Malignancy; ADM, AIDS-Defining Malignancy; HE, HAART Era; PH, pre-HAART Era

B)

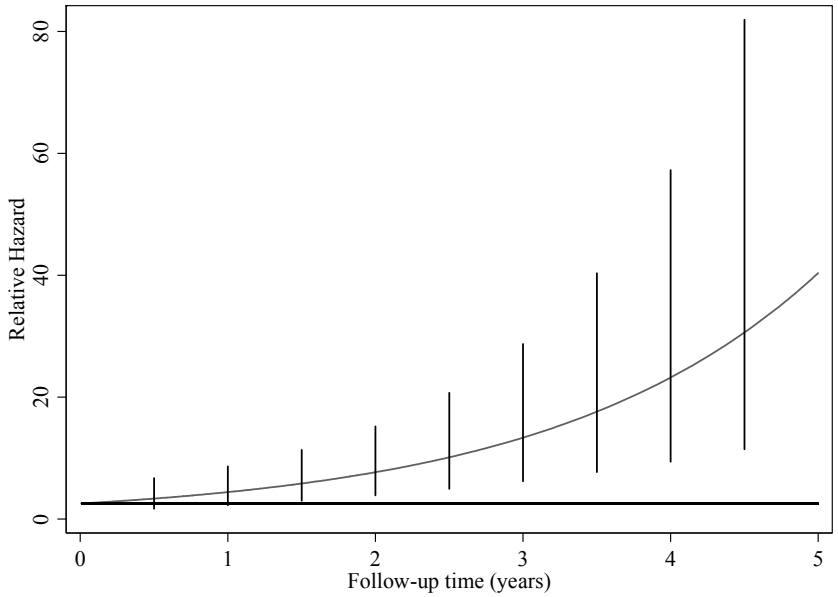


Table 5. Univariable Cox Proportional Hazards Models of Mortality Comparing Cancer Survival Among HIV-infected Individuals Diagnosed with Cancer in the pre-HAART (1984-1994) and the HAART (1995-2013) Eras

	HR	95% CI	p-value[a]
Cancer Type			
NADM	REF		
ADM	4.70	3.17, 6.97	**<0.001**
Cancer Type			
Non-Infection-Related	REF		
Infection-Related	4.41	2.67, 7.29	**<0.001**
Era			
Pre-HAART	REF		
HAART	0.22	0.16, 0.30	**<0.001**
Age (years)			
< 30	1.08	0.86, 1.34	0.51
30 - 39	1.59	1.11, 2.28	**0.01**
40 - 49	REF		
50 - 59	0.43	0.28, 0.64	**<0.001**
60 +	0.16	0.05, 0.49	**<0.001**
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	0.63	0.41, 0.95	**0.03**
Other	1.22	0.86, 1.72	0.27
IDU			
Never/Former	REF		
Current	0.76	0.31, 1.83	0.54
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.63	0.99, 2.70	0.06
Overweight/Obese (25.0 +)	0.54	0.41, 0.70	**<0.001**
Smoking History			
Never/Former	REF		
Current	1.04	0.84, 1.30	0.70
Prior AIDS Diagnosis			
No	REF		
Yes	2.11	1.68, 2.64	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	4.83	3.34, 7.00	**<0.001**
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	2.58	2.02, 3.29	**<0.001**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

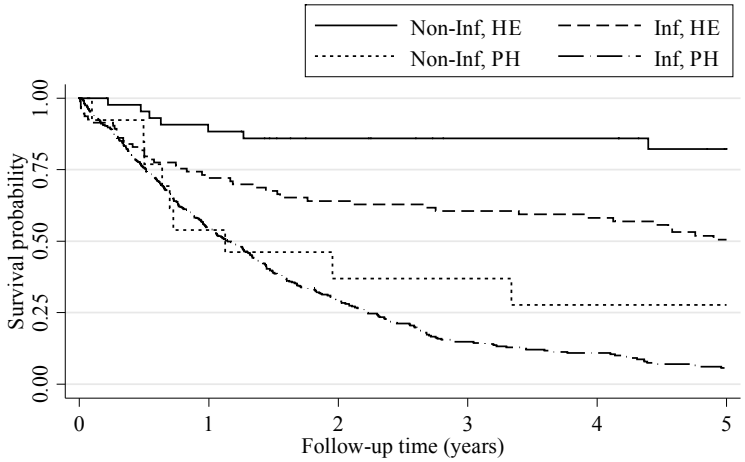
Table 6. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival Among HIV-infected Individuals Diagnosed with Non-AIDS-Defining Malignancies (NADMs) and AIDS-Defining Malignancies (ADMs) in the pre-HAART (1984-1994) and the HAART (1995-2013) Eras

	HR	95% CI	p-value[a]
Cancer Type and Era			
NADM, HAART era	REF		
ADM, HAART era	2.12	1.08, 4.15	**0.03**
NADM, pre-HAART era	4.91	2.12, 11.39	**<0.001**
ADM, pre-HAART era	2.54	1.22, 5.30	**0.01**
Interaction with time for ADM, pre-HAART era	1.74	1.38, 2.19	**<0.001**
Age (years)			
< 30	REF		
30 - 39	0.76	0.53, 1.09	0.13
40 - 49	0.89	0.61, 1.28	0.52
50 - 59	0.83	0.48, 1.42	0.50
60 +	0.70	0.19, 2.56	0.59
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	1.00	0.65, 1.54	1.00
Other	1.22	0.86, 1.75	0.27
IDU			
Never/Former	REF		
Current	0.67	0.27, 1.68	0.40
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.51	0.90, 2.53	0.12
Overweight/Obese (25.0 +)	0.75	0.57, 0.99	**0.05**
Smoking History			
Never/Former	REF		
Current	1.33	1.06, 1.66	**0.01**
Prior AIDS Diagnosis			
No	REF		
Yes	1.83	1.44, 2.34	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.38	0.85, 2.21	0.19
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	2.35	1.79, 3.08	**<0.001**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

Figure 5. A) 5-Year Unadjusted Cancer Survival Plot by HAART Era and Cancer Type (Infection-Related or Non-Infection-Related) Among HIV-infected participants in the MACS, B) Plot of the Relative Hazard as a Function of Time Comparing Survival for Participants Diagnosed with Infection-Related Cancers in the pre-HAART Era (Inf, PH) relative to Participants Diagnosed with Non-Infection-Related Cancers in the HAART Era (Non-Inf, HE)

A)



Number at risk						
Non-Inf, HE	44	38	31	26	26	20
Inf, HE	94	66	55	52	48	36
Non-Inf, PH	13	7	4	4	2	1
Inf, PH	405	208	98	38	25	11

Abbreviations: Non-Inf, Non-Infection-Related Cancer; Inf, Infection-Related Cancer; HE, HAART Era; PH, pre-HAART Era

B)

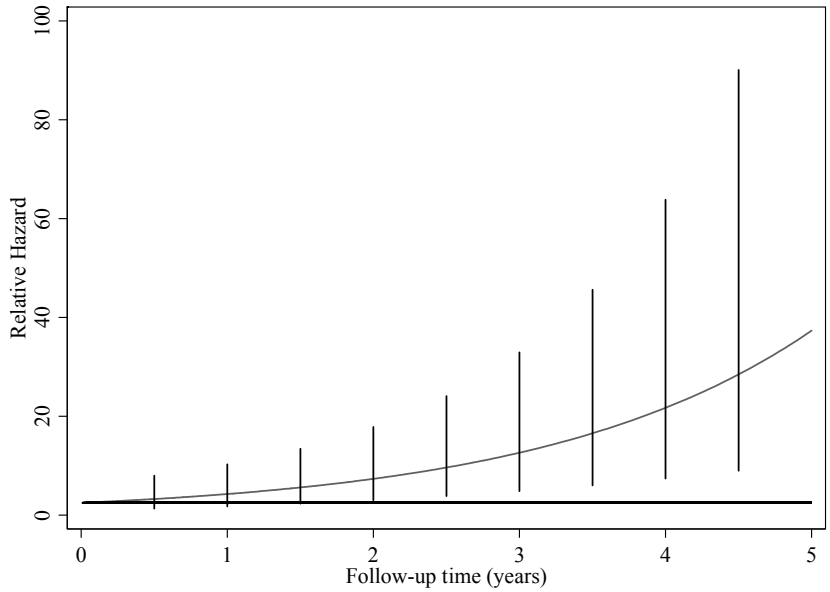
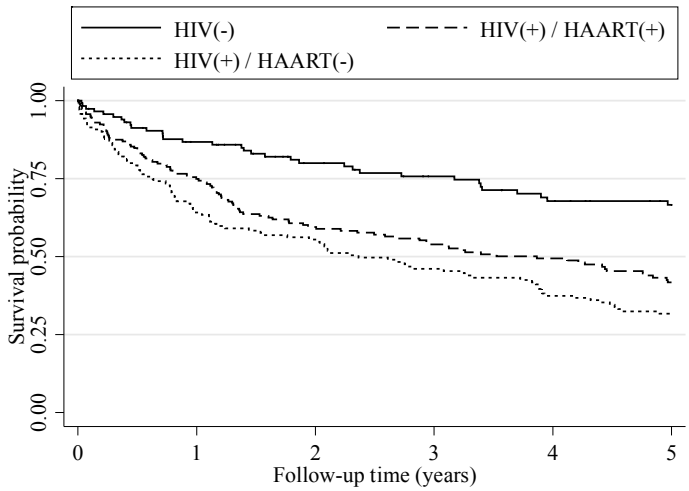


Table 7. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival Among HIV-infected Individuals Diagnosed with Infection-Related Cancers and Non-Infection-Related Cancers in the pre-HAART (1984-1994) and the HAART (1995-2013) Eras

	HR	95% CI	p-value[a]
Cancer Type and Era			
Non-Infection-Related, HAART era	REF		
Infection-Related, HAART era	1.89	0.81, 4.39	0.14
Non-Infection-Related, pre-HAART era	6.56	2.33, 18.48	**<0.001**
Infection-Related, pre-HAART era	2.48	0.98, 6.29	0.06
Interaction with time for infection-related, pre-HAART	1.72	1.36, 2.18	**<0.001**
Age (years)			
< 30	REF		
30 - 39	0.76	0.54, 1.09	0.14
40 - 49	0.88	0.61, 1.28	0.51
50 - 59	0.79	0.46, 1.36	0.39
60 +	0.59	0.17, 2.08	0.41
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	0.95	0.62, 1.46	0.82
Other	1.23	0.87, 1.76	0.24
IDU			
Never/Former	REF		
Current	0.71	0.29, 1.78	0.47
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.53	0.91, 2.57	0.11
Overweight/Obese (25.0 +)	0.75	0.57, 0.99	**0.04**
Smoking History			
Never/Former	REF		
Current	1.32	1.05, 1.65	**0.02**
Prior AIDS Diagnosis			
No	REF		
Yes	1.81	1.42, 2.31	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.57	0.98, 2.51	0.06
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	2.38	1.82, 3.12	**<0.001**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

Figure 6. 5-Year Unadjusted Cancer Survival Plot by HIV Status and HAART Use Among MACS and WIHS participants in the HAART Era



Number at risk						
HIV(-)	115	95	77	68	59	52
HIV(+) / HAART(+)	184	136	99	85	76	54
HIV(+) / HAART(-)	140	89	77	64	52	44

Table 8. Univarible Cox Proportional Hazards Models of Mortality Comparing Cancer Survival Use Among HIV-infected and –uninfected MACS and WIHS participants in the HAART (1995-2013) Era

	HR	95% CI	p-value[a]
HIV Infection			
No	REF		
Yes	2.42	1.68, 3.49	**<0.001**
HAART Experienced			
No	REF		
Yes	1.12	0.87, 1.46	0.38
Age (years)			
< 30	0.82	0.56, 1.19	0.29
30 - 39	1.20	0.44, 3.27	0.72
40 - 49	REF		
50 - 59	0.80	0.59, 1.09	0.16
60 +	0.42	0.26, 0.67	**<0.001**
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	2.51	1.87, 3.37	**<0.001**
Other	2.14	1.46, 3.14	**<0.001**
IDU			
Never/Former	REF		
Current	1.89	0.93, 3.83	0.08
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	2.64	1.65, 4.24	**<0.001**
Overweight/Obese (25.0 +)	0.83	0.63, 1.08	0.17
Smoking History			
Never/Former	REF		
Current	2.16	1.66, 2.82	**<0.001**
Prior AIDS Diagnosis			
No	REF		
Yes	2.72	2.10, 3.53	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.86	1.43, 2.43	**<0.001**
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	1.94	1.49, 2.51	**<0.001**

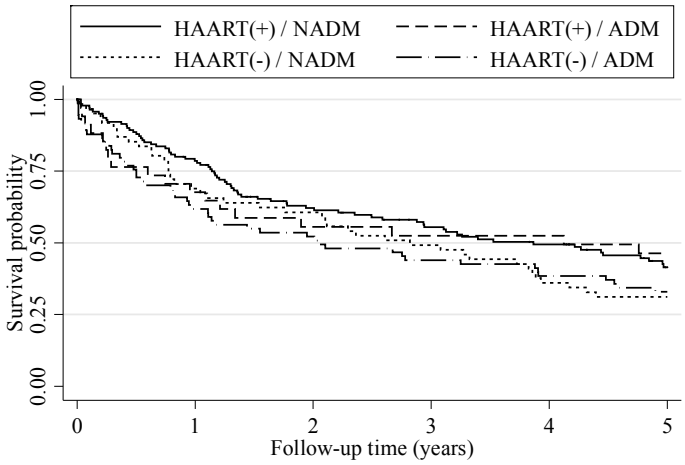
Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

Table 9. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival by HIV Status and HAART Use Among MACS and WIHS participants in the HAART (1995-2013) Era

	HR	95% CI	p-value[a]
HIV Status and HAART Use			
HIV(-)	REF		
HIV(+) using HAART	0.92	0.57, 1.48	0.72
HIV(+) not using HAART	1.26	0.78, 2.05	0.34
Age (years)			
< 30	REF		
30 - 39	0.97	0.33, 2.86	0.96
40 - 49	1.26	0.44, 3.57	0.67
50 - 59	1.38	0.48, 3.96	0.56
60 +	1.18	0.39, 3.60	0.77
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	1.36	0.94, 1.97	0.10
Other	1.03	0.66, 1.61	0.89
IDU			
Never/Former	REF		
Current	0.84	0.40, 1.76	0.64
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.42	0.86, 2.35	0.17
Overweight/Obese (25.0 +)	0.76	0.57, 1.02	0.07
Smoking History			
Never/Former	REF		
Current	1.35	1.00, 1.83	**0.05**
Prior AIDS Diagnosis			
No	REF		
Yes	1.55	1.13, 2.13	**0.007**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.15	0.82, 1.60	0.42
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	1.44	1.01, 2.04	**0.04**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.
Note: Model stratified by cohort.

Figure 7. 5-Year Unadjusted Cancer Survival Plot by Cancer Type (ADM vs. NADM) and HAART Use Among HIV-infected MACS and WIHS participants in the HAART Era



Number at risk						
HAART(+) / NADM	141	109	78	65	56	37
HAART(+) / ADM	34	23	18	17	17	15
HAART(-) / NADM	61	42	37	30	22	19
HAART(-) / ADM	74	45	38	32	28	24

Abbreviations: NADM, Non-AIDS-Defining Malignancy; ADM, AIDS-Defining Malignancy

Table 10. Univariable Cox Proportional Hazards Models of Mortality Comparing Cancer Survival Among HIV-infected MACS and WIHS participants in the HAART (1995-2013) Era

	HR	95% CI	p-value[a]
Cancer Type			
NADM	REF		
ADM	1.15	0.85, 1.55	0.36
Cancer Type			
Non-Infection-Related	REF		
Infection-Related	1.01	0.75, 1.34	0.96
HAART Experienced			
No	REF		
Yes	0.74	0.56, 0.99	**0.04**
Age (years)			
< 30	0.81	0.55, 1.20	0.29
30 - 39	1.70	0.54, 5.39	0.37
40 - 49	REF		
50 - 59	0.82	0.58, 1.16	0.25
60 +	0.56	0.29, 1.04	0.07
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	2.25	1.61, 3.14	**<0.001**
Other	1.72	1.12, 2.64	**0.01**
IDU			
Never/Former	REF		
Current	1.85	0.91, 3.76	0.09
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	2.49	1.50, 4.16	**<0.001**
Overweight/Obese (25.0 +)	0.85	0.63, 1.15	0.30
Smoking History			
Never/Former	REF		
Current	1.62	1.21, 2.16	**0.001**
Prior AIDS Diagnosis			
No	REF		
Yes	2.42	1.80, 3.24	**<0.001**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.57	1.18, 2.10	**0.002**
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	1.65	1.22, 2.23	**0.001**

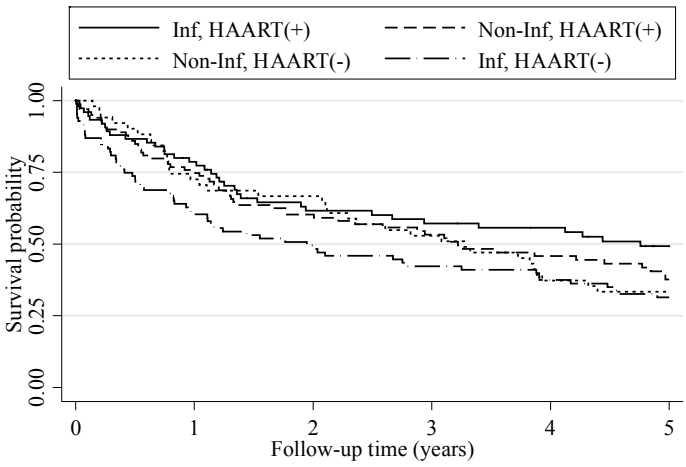
Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.

Table 11. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival by Cancer Type (ADM vs. NADM) and HAART Use Among HIV-infected MACS and WIHS participants in the HAART (1995-2013) Era

	HR	95% CI	p-value[a]
Cancer Type			
NADM	REF		
ADM	1.36	0.90, 2.05	0.14
HAART Use			
No	REF		
Yes	0.68	0.48, 0.96	**0.03**
Age (years)			
< 30	REF		
30 - 39	0.76	0.22, 2.70	0.68
40 - 49	1.10	0.31, 3.86	0.88
50 - 59	1.16	0.32, 4.16	0.83
60 +	0.99	0.25, 3.98	0.99
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	1.66	1.09, 2.52	**0.02**
Other	1.10	0.67, 1.79	0.71
IDU			
Never/Former	REF		
Current	0.83	0.39, 1.78	0.63
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.36	0.79, 2.37	0.27
Overweight/Obese (25.0 +)	0.70	0.50, 0.97	**0.03**
Smoking History			
Never/Former	REF		
Current	1.08	0.77, 1.51	0.67
Prior AIDS Diagnosis			
No	REF		
Yes	1.68	1.20, 2.35	**0.002**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.00	0.68, 1.47	1.00
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	1.53	1.05, 2.22	**0.03**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.
Note: Model stratified by cohort.

Figure 8. 5-Year Unadjusted Cancer Survival Plot by Cancer Type (infection-related vs. non-infection related) and HAART Use Among HIV-infected MACS and WIHS participants in the HAART Era



Number at risk						
Inf, HAART(+)	75	58	42	39	36	26
Non-Inf, HAART(+)	100	74	54	43	37	26
Non-Inf, HAART(-)	51	37	34	27	19	17
Inf, HAART(-)	84	50	41	35	31	26

Abbreviations: Non-Inf, Non-Infection-Related Cancer; Inf, Infection-Related Cancer

Table 12. Multivariable Cox Proportional Hazards Model of Mortality Comparing Cancer Survival by Cancer Type (infection-related vs. non-infection-related) and HAART Use Among HIV-infected MACS and WIHS participants in the HAART Era

	HR	95% CI	p-value[a]
Cancer Type			
Non-Infection-Related	REF		
Infection-Related	1.98	1.18, 3.32	**0.01**
HAART Use			
No	REF		
Yes	1.07	0.67, 1.72	0.77
Interaction between HAART Use and Infection-Related	0.36	0.19, 0.69	**0.002**
Age (years)			
< 30	REF		
30 - 39	0.62	0.18, 2.18	0.46
40 - 49	0.89	0.26, 3.03	0.85
50 - 59	0.90	0.26, 3.14	0.87
60 +	0.87	0.22, 3.41	0.84
Race			
White, non-Hispanic	REF		
Black, non-Hispanic	1.79	1.17, 2.74	**0.007**
Other	1.11	0.68, 1.81	0.68
IDU			
Never/Former	REF		
Current	0.67	0.31, 1.46	0.32
BMI			
Normal (18.5 – 24.9)	REF		
Underweight (< 18.5)	1.36	0.78, 2.38	0.27
Overweight/Obese (25.0 +)	0.66	0.48, 0.92	**0.01**
Smoking History			
Never/Former	REF		
Current	1.14	0.81, 1.60	0.46
Prior AIDS Diagnosis			
No	REF		
Yes	1.71	1.22, 2.40	**0.002**
Viral Load (cp/ml)			
< 10,000	REF		
> 10,000	1.05	0.72, 1.54	0.79
Nadir CD4 Cell Count (cells/µl)			
> 200	REF		
< 200	1.48	1.01, 2.14	**0.04**

Abbreviations: IDU, intravenous drug user; BMI, body mass index (kg/m^2)
[a]Pearson's χ^2 was used for categorical variables.
Note: Model stratified by cohort

Table 13. Adjusted Cox Proportional Hazards Ratios of Mortality Comparing Cancer Survival by Cancer Type (infection-related vs. non-infection-related) and HAART Use Among HIV-infected MACS and WIHS participants in the HAART Era

	HR	**95% CI**	**p-value**[a]
HAART Users (REF) to Non-Users			
Non-Infection-Related	1.07	0.67, 1.72	0.29
Infection-Related	0.36	0.19, 0.69	**0.002**
Infection-Related (REF) to Non-Infection-Related			
Non-HAART Users	1.98	1.18, 3.32	**0.01**
HAART Users	0.71	0.44, 1.13	0.15

[a]Pearson's χ^2 was used for categorical variables.
Note: Model stratified by cohort

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CURRICULUM VITAE

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EDUCATION

Master of Science (ScM), GPA: 4.0 / 4.0 **Expected May 2015**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: General Epidemiology and Methodology
Relevant Coursework: Epidemiological Methods 1-3, Methodological Challenges in Epidemiological Research, Statistical Methods 1-4, Etiology, Prevention & Control of Cancer, Spatial Analysis/GIS I & II, Advanced Methods for Design and Analysis of Cohort Studies, Data Management, Epidemiology and the Public Health Impact of HIV/AIDS, Longitudinal Data Analysis, Causal Inference in Medicine, The SAS Package for Statisticians

Bachelor of the Arts (BA) in Biological Sciences, GPA: 3.89 / 4.0 **May 2011**
Rutgers University, New Brunswick, NJ: School of Arts & Sciences
Honors Program
Minor: English
Honors: Summa Cum Laude, Highest Departmental Honors in Biological Sciences, School of Arts and Sciences Honors Scholar, Betty Falk Yatvin Award (2011), Phi Beta Kappa, Dean's List (every semester), School of Arts & Sciences Excellence Award (2008-2009), Rutgers Academic Excellence Award (2009)

RESEARCH EXPERIENCE

Graduate Student Researcher **June 2014- present**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Composed and submitted a research proposal that was accepted by the Multicenter AIDS Cohort Study (MACS) and Women's Integrative HIV Study (WIHS) committees
- Completed a thesis project on cancer survival involving the MACS and WIHS cohorts (Dr. Eric Seaberg)

Undergraduate Student Researcher **Jun. 2009 – May 2011**
Rongo Lab, Waksman Institute of Microbiology, Piscataway, NJ

- Optimized behavioral assays for associative learning defective *C. elegans* mutants in preparation for whole genome sequencing
- Investigated CyPD function for its role in stress resistance, aging, and mitochondrial cell biology
- Defended senior thesis in front of a life sciences faculty members committee & earned Highest Departmental Honors
- Presented at the Aresty Undergraduate Research Symposium (2011) and the Rutgers Day Research Symposium (2011)

WORK EXPERIENCE

Office Manager **Mar. 2012 – Jul. 2013**

Reisner Orthodontics, Karen Reisner, DDS, Cresskill, NJ

- Ran, organized, and maintained the front desk of the orthodontic practice
- Managed patients' financial accounts using the Orthotrac software and Excel spreadsheets, and assisted with the technological demands of the office (including composition of electronic newsletters, office marketing via social media, and troubleshooting of software associated with dental equipment)
- Handled all matters related to dental insurance (i.e. checked coverage for patients, prepared and followed up on insurance claims)

Volunteer EMT **Oct. 2011 – Mar. 2013**

Teaneck Volunteer Ambulance Corps (TVAC), Teaneck, NJ

- Assisted members of the community with medical emergencies on a weekly shift and on special occasions for which the town requests an ambulance standby
- As a member of the social committee, helped plan, organize, and run the TVAC Gala (the main fundraising event)

TEACHING EXPERIENCE

Teaching Assistant (TA) **July 2014 - present**

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course Title: Principles of Epidemiology (340.601), **Terms:** Summer 2014, Fall 2014

- Led and assisted with laboratory sessions twice a week in a section of 60+ students
- Held office hours to assist students with course material and review questions in preparation for the exams
- Partook in weekly staff meetings and attended course lectures
- Graded written assignments, and proctored and graded both the midterm and final exams

Course Title: Stata Programming (340.600), **Terms:** Spring 2015

- Holds office hours to assist students with course material and homework assignments
- Grades homework assignments and attends course lectures

PROFESSIONAL DEVELOPMENT

Language Skills: Fluent English, Hebrew, Spanish (5 years of study)
Computer Skills: Proficient in MS Word, Excel, PowerPoint, Stata, research search engines such as PubMed; Experience in ArcGIS, SAS, REDCap, SQL
Lab Techniques: subcloning, aging studies, behavioral studies, site-directed mutagenesis, RNAi, microscopy

ACTIVITIES

Rutgers Democrats Secretary (2009-2010), Rutgers Hebrew Club Executive Board (2009-2011), Shalom/Salaam (2010-2011), Bicycle Touring Club of North Jersey (2012-2013), Jewish Graduate Student Association of Johns Hopkins (Sept. 2014 – present)